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Efficacy of Sofosbuvir, Velpatasvir, and GS-9857 in Patients With Hepatitis C Virus Genotype 2, 3, 4, or 6 Infections in an Open-Label, Phase 2 Trial

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BACKGROUND & AIMS: Studies are needed to determine the optimal regimen for patients with chronic hepatitis C virus (HCV) genotype 2, 3, 4, or 6 infections whose prior course of antiviral therapy has failed, and the feasibility of shortening treatment duration. We performed a phase 2 study to determine the efficacy and safety of the combination of the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the NS3/4A protease inhibitor GS-9857 in these patients. **METHODS:** We performed a multicenter, open-label trial at 32 sites in the United States and 2 sites in New Zealand from March 3, 2015 to April 27, 2015. Our study included 128 treatment-naïve and treatment-experienced patients (1 with HCV genotype 1b; 33 with HCV genotype 2; 74 with HCV genotype 3; 17 with genotype HCV 4; and 3 with HCV genotype 6), with or without compensated cirrhosis. All patients received sofosbuvir-velpatasvir (400 mg/100 mg fixed-dose combination tablet) and GS-9857 (100 mg) once daily for 6–12 weeks. The primary end point was sustained virologic response 12 weeks after treatment (SVR12). **RESULTS:** After 6 weeks of treatment, SVR12s were achieved by 88% of treatment-naïve patients without cirrhosis (29 of 33; 95% confidence interval, 72%–97%). After 8 weeks of treatment, SVR12s were achieved by 93% of treatment-naïve patients with cirrhosis (28 of 30; 95% CI, 78%–99%). After 12 weeks of treatment, SVR12s were achieved by all treatment-experienced patients without cirrhosis (36 of 36; 95% CI, 90%–100%) and 97% of treatment-experienced patients with cirrhosis (28 of 29; 95% CI, 82%–100%). The most common adverse events were headache, diarrhea, fatigue, and nausea. Three patients (1%) discontinued treatment due to adverse events. **CONCLUSIONS:** In a phase 2 open-label trial, we found sofosbuvir-velpatasvir plus GS-9857 (8 weeks in treatment-naïve patients or 12 weeks in treatment-experienced patients) to be safe and effective for patients with HCV genotype 2, 3, 4, or 6 infections, with or without compensated cirrhosis. ClinicalTrials.gov ID: NCT02378961.

Keywords: Clinical Trial; Direct-Acting Antiviral; DAA; Non-Genotype 1 HCV.

It is estimated that at least 80–185 million people are chronically infected with the hepatitis C virus (HCV) worldwide.[1–3] Although genotype 1 HCV is the most common strain of the virus, genotypes 2–6 cumulatively account for more than half of those infected worldwide, or approximately 60 million people.[1] The global prevalence of these HCV genotypes varies widely, and they are characterized by differential rates of disease progression, hepatocellular carcinoma risk, and response to treatment.[2] Across the world, genotype 3 HCV is the second most common strain, representing 30% of HCV infections, followed by genotype 2

[†]Deceased.

Abbreviations used in this paper: **CI, confidence interval; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; RAS, resistance-associated substitution; SVR, sustained virologic response; SVR12, sustained virologic response 12 weeks after treatment.**

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(9%), genotype 4 (8%), genotype 6 (5%), and genotype 5 (1%).[1] Regimens of recently approved direct-acting antiviral agents (DAAs) have been shown to provide high rates of sustained virologic response (SVR) in patients infected by any of the 6 genotypes.[4,5] A small proportion of patients, however, do not achieve SVR with existing regimens, particularly those who have previously failed treatment with a prior DAA agent, in whom resistance-associated substitutions (RASs) may have emerged to first-generation NS3/4A and NS5A inhibitors.[6] Retreatment options for these patients are limited. One possible retreatment strategy to address this growing unmet need is to combine 3 highly potent DAAs with different mechanisms of action that retain antiviral activity against these emergent RASs. Such a 3-DAA combination regimen might also allow for the shortening of treatment duration to <12 weeks in patients who have not been treated previously for HCV, and improvement of efficacy for patients with genotype 3 and cirrhosis, which is a more difficult-to-treat population with current therapies.[7–9]

Sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B polymerase approved for the treatment of genotypes 1–4 HCV infection in combination with other agents.[10,11] Velpatasvir is a novel HCV NS5A inhibitor with pan-genotypic efficacy.[12] The combination of sofosbuvir and velpatasvir has been demonstrated in phase 3 clinical trials to be highly effective and safe in treatment-naïve and previously treated patients with HCV of all genotypes, including those with compensated and decompensated cirrhosis.[13–15] GS-9857 is a novel macrocyclic NS3/4A protease inhibitor with potent in vitro antiviral activity against genotypes 1 to 6 HCV and broad coverage of NS3/4A protease polymorphisms.[16–19] In a phase 1 trial, administration of 100 mg GS-9857 to patients with genotype 1–4 HCV resulted in median maximum reductions in HCV RNA of ≥3 log10 IU/mL.[16]

We assessed the efficacy and safety of 6–12 weeks of sofosbuvir-velpatasvir plus GS-9857 in treatment-naïve and previously treated patients with non–genotype 1 HCV, including those with compensated cirrhosis.

Methods

Study Design

This open-label, 2-cohort, phase 2 study was conducted between March 3, 2015 and April 27, 2015 at 32 sites in the United States and 2 sites in New Zealand. Cohort 1 enrolled treatment-naïve patients and cohort 2 enrolled treatment-experienced patients. All patients received sofosbuvir-velpatasvir plus GS-9857.

Cohort 1

Treatment-naïve patients in cohort 1 without cirrhosis received 6 weeks of treatment, while patients with cirrhosis received 8 weeks of treatment. The protocol specified that if the rate of relapse among treatment-naïve patients with cirrhosis who received 8 weeks of treatment was ≤10%, another group could optionally be enrolled to receive 6 weeks of treatment. This option was not exercised.

Cohort 2

Cohort 2 consisted of treatment-experienced patients, including those who had been treated with DAAs, with or without interferon. Regardless of cirrhosis status, all patients received 12 weeks of treatment. If the relapse rate of cohort 2 was ≤10%, another group could optionally be enrolled to receive 8 weeks of treatment. This option was not exercised.

Patients

Enrollment was open to patients at least 18 years of age chronically infected with genotypes 2, 3, 4, 5, or 6 HCV with serum HCV RNA viral loads of at least 10,000 IU/mL. Target enrollment for patients with genotype 3 HCV was 50% in each treatment group. Given the low prevalence of genotypes 4, 5, or 6 HCV infections in the United States, there were no minimum enrollment criteria for these patients. Cirrhosis was defined as any one of the following: biopsy showing cirrhosis (Metavir score of 4 or Ishak score of ≥5), transient elastography (FibroScan) result of >12.5 kPa, or a FibroTest score of >0.75, together with an aspartate transaminase to platelet ratio index of >2 during screening. Exclusion criteria included platelet count <50,000 cells/μL, hemoglobin <110 g/L for women and <120 g/L for men, albumin <30 g/L, creatinine clearance <60 mL/min as calculated by the Crockoft-Gault equation, and prothrombin time or direct bilirubin of <1.5 times the upper limit of normal. Patients with evidence of decompensation (ie, clinical ascites, encephalopathy, or variceal hemorrhage) and those with hepatocellular carcinoma were excluded.

Written informed consent was obtained from all patients before enrollment and before any study procedures were undertaken. The study was approved by the Institutional Review Board or independent ethics committees at all participating sites and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The sponsor (Gilead Sciences) collected the data, monitored the study conduct, and performed the statistical analyses.

Procedures

All patients received a fixed-dose combination tablet of sofosbuvir 400 mg and velpatasvir 100 mg once daily, along with a 100 mg tablet of GS-9857 once daily, taken with food.

Randomization and masking

This was a nonrandomized, open-label study. Investigators at the study centers enrolled patients until the target enrollment was reached, including minimum numbers of patients with genotype 3 HCV infection. No participants or study personnel were blinded to treatment assignments at any time during the study.

Assessments

Serum HCV RNA concentrations were measured using the COBAS AmpliPrep/COBAS TaqMan HCV Test, version 2.0 (Roche, Indianapolis, IN) with a lower limit of quantification for HCV RNA of <15 IU/mL. HCV genotype and subtype was determined using the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 assay. For all patients, the interleukin 28B genotype was determined by polymerase chain reaction

amplification and sequencing of the rs12979860 single nucleotide polymorphism.

Deep sequencing of the NS3A, NS5A, and NS5B regions of the HCV RNA using MiSeq technology (DDL Diagnostic Laboratory, Rijswijk, The Netherlands) was performed at baseline for all patients and at the time of virologic failure for all patients who did not achieve sustained virologic response 12 weeks after treatment (SVR12). The resulting sequences were compared with reference sequences or sequences from baseline samples in order to determine the prevalence of RASs and the association of RASs with virologic outcomes. RASs present at >1% of sequence reads are reported.

Safety was assessed in all patients at all on-treatment visits and for 30 days after the completion of treatment by physical examination and review of adverse events and blood samples for clinical laboratory testing.

Outcomes

The primary efficacy end point of this study was SVR12 (serum HCV RNA <15 IU/mL) in all patients who were enrolled and received at least 1 dose of study drug. The secondary efficacy end points included proportion of patients with virologic failure. The primary safety end point was any adverse event leading to the permanent discontinuation of study treatment.

Statistical Analysis

For this exploratory phase 2 study, we did not plan or conduct any inferential statistics. No formal sample size calculations were used to determine the group size of 30. The SVR12 rate in each of the treatment groups was calculated with 2-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method.

Role of the funding source

The study sponsor oversaw trial management, data collection, statistical analyses, and the writing and review of the report. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Of the 171 patients screened, 128 were enrolled and received treatment: 33 treatment-naïve patients without cirrhosis, 30 treatment-naïve patients with cirrhosis, 36 previously treated patients without cirrhosis, and 29 previously treated patients with cirrhosis (Figure 1). Reasons for screen failure are listed in the Supplementary Table 1. Baseline characteristics of patients are given in Table 1. In total, the study enrolled, 33 (26%) patients with genotype 2 HCV, 74 (58%) patients with genotype 3 HCV, 17 (13%) patients with genotype 4 HCV, and 3 (2%) patients with genotype 6 HCV. No patient with genotype 5 HCV was enrolled. There was 1 patient who was genotype 1b by LiPA genotyping assay at screening who was enrolled based on a history of genotype 6 infection, as allowed per protocol; this was a treatment-naïve patient without cirrhosis who

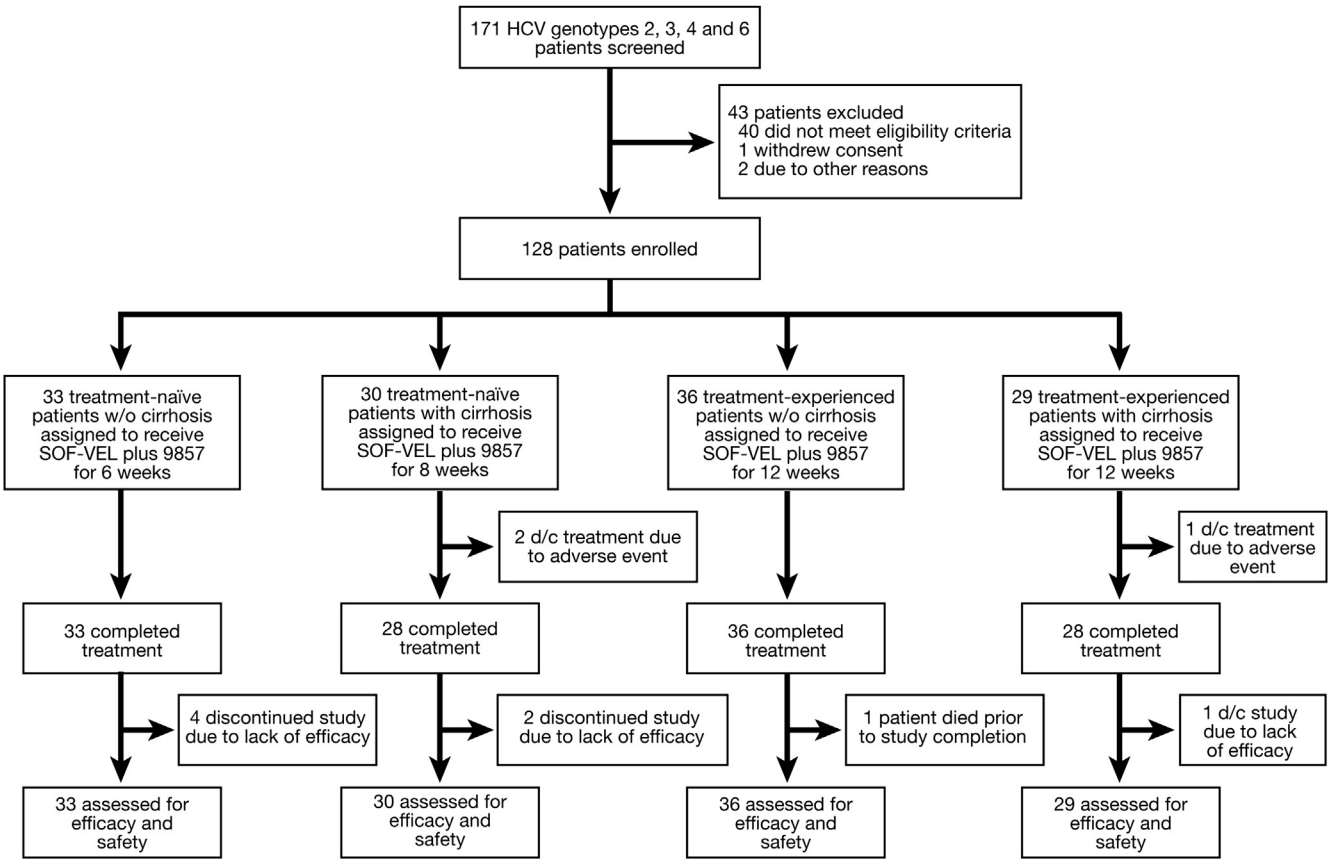

Figure 1. Patient disposition.

Table 1. Baseline Characteristics

Characteristic	Treatment-naïve		Treatment-experienced	
	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
	SOF-VEL + GS-9857 for 6 wk (n = 33)	SOF-VEL + GS-9857 for 8 wk (n = 30)	SOF-VEL + GS-9857 for 12 wk (n = 36)	SOF-VEL + GS-9857 for 12 wk (n = 29)
Age, *y*	53	56	57	58
Men, n (%)	12 (36)	21 (70)	26 (72)	21 (72)
Race, n (%)				
White	27 (82)	24 (80)	29 (81)	23 (79)
Black	2 (6)	1 (3)	2 (6)	2 (7)
Asian	3 (9)	4 (13)	3 (8)	2 (7)
Other	1 (3)	1 (3)	2 (6)	0
BMI, kg/m^2, mean (SD)	26.9 (5.8)	29.8 (5.3)	27.3 (4.9)	30.8 (7.0)
HCV RNA, log_{10} *IU/mL*, mean (SD)	6.2 (0.9)	6.1 (0.7)	6.3 (0.7)	6.4 (0.6)
HCV genotype, n (%)				
1b	1 (3)[a]	0	0	0
2	6 (18)	6 (20)	13 (36)	8 (28)
3	21 (64)	18 (60)	18 (50)	17 (59)
4	5 (15)	5 (17)	4 (11)	3 (10)
6	0	1 (3)	1 (3)	1 (3)
IL28b, n (%)				
CC	11 (33)	11 (37)	15 (42)	10 (35)
CT	15 (45)	15 (50)	15 (42)	17 (59)
TT	6 (18)	4 (13)	5 (14)	2 (7)
Missing	1 (3)	0	1 (3)	0
Treatment experience, n (%)				
No DAA	—	—	17 (47)	10 (34)
SOF + RBV ± PEG			14 (39)	17 (59)
Other DAAs	—	—	5 (14)	2 (7)

BMI, body mass index; PEG, peginterferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.
[a]This patient was enrolled into the study with historical genotype 6, as was allowed by protocol. At screening, the patient was found to have genotype 1b.

received 6 weeks of treatment and achieved SVR12 and will not be discussed further. The groups were balanced overall, other than in sex; women made up 64% of treatment-naïve patients without cirrhosis but only 28%–30% in the other treatment groups. Among the 65 treatment-experienced patients in cohort 2, 53% of the 36 without cirrhosis and 66% of the 29 with cirrhosis, patients had previously received at least 1 DAA. Most treatment-experienced patients had received sofosbuvir-containing regimens (Table 1). Details concerning prior HCV treatment regimens are given in the Supplementary Table 2.

By week 4 of treatment, all 63 treatment-naïve patients—including those with and without cirrhosis—had HCV RNA <15 IU/mL. Among treatment-experienced patients, 11% of those without cirrhosis and 10% of those with cirrhosis still had detectable HCV RNA (>15 IU/mL) at week 4 of treatment. By week 8 of treatment, all 65 treatment-experienced patients had undetectable HCV RNA. Table 2 summarizes information about patients with HCV RNA <15 IU/mL during and after treatment.

Among treatment-naïve patients, rates of SVR12 were 88% (29 of 33; 95% CI, 72%–97%) in patients without cirrhosis receiving 6 weeks of treatment, and 93% (28 of 30; 95% CI, 78%–99%) in patients with cirrhosis receiving 8 weeks of treatment (Table 2). Treatment-naïve patients with HCV genotype 3 and cirrhosis who received 8 weeks of treatment had an SVR12 rate of 94% (17 of 18; 95% CI, 73%–100%).

Among treatment-experienced patients treated for 12 weeks, rates of SVR12 were 100% (36 of 36; 95% CI, 90%–100%) in patients without cirrhosis, and 97% (28 of 29; 95% CI, 82%–100%) in patients with cirrhosis. Treatment-experienced patients with HCV genotype 3 and cirrhosis who received 12 weeks of treatment had an SVR12 rate of 94% (16 of 17; 95% CI, 71%–100%). Among patients who had previously received a DAA, rates of SVR12 were 100% (19 of 19; 95% CI, 82%–100%) in those without cirrhosis and 95% (18 of 19; 95% CI, 74%–100%) in those with cirrhosis.

Across the groups, SVR12 rates did not significantly vary by baseline characteristics (Supplementary Table 3). Across treatment groups, rates of SVR12 were 94% (31 of 33) for patients with genotype 2 HCV, 97% (72 of 74) for patients with genotype 3 HCV, and 82% (14 of 17) for patients with genotype 4 HCV (Table 2). All 3 patients with genotype 6 achieved SVR12.

All 7 patients who did not achieve SVR12 had virologic relapse (Supplementary Table 4). The highest rates of

Table 2. Patients with Hepatitis C Virus RNA <15 IU/mL During and After Treatment

	Treatment-naïve		Treatment-experienced	
	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Variable	SOF-VEL + GS-9857 for 6 wk (n = 33)	SOF-VEL + GS-9857 for 8 wk (n = 30)	SOF-VEL + GS-9857 for 12 wk (n = 36)	SOF-VEL + GS-9857 for 12 wk (n = 29)
HCV RNA <LLOQ				
During treatment				
Wk 2	27 (82)	22 (73)	26 (72)	17 (59)
Wk 4	33 (100)	30 (100)	32 (89)	26 (90)
After treatment				
Wk 4	30 (91)	29 (97)	36 (100)	29 (100)
Wk 12 (SVR12)	29 (88)	28 (93)	36 (100)	28 (97)
95% CI	72 to 97	78 to 99	90 to 100	82 to >99
SVR12 by genotype				
1b	1[a] (100)	0	0	0
2	4/6 (67)	6/6 (100)	13/13 (100)	8/8 (100)
3	21/21 (100)	17/18 (94)	18/18 (100)	16/17 (94)
4	3/5 (60)	4/5 (80)	4/4 (100)	3/3 (100)
6	0	1/1 (100)	1/1 (100)	1/1 (100)
Virologic failure				
Relapse	4 (12)	2 (7)	0	1 (3)

NOTE. Values are n (%).
LLOQ, lower limit of quantification; SOF, sofosbuvir; VEL, velpatasvir.
[a]This patient was enrolled into the study with historical genotype 6, as was allowed by protocol. At screening, the patient was found to have genotype 1b.

relapse were observed among treatment-naïve patients with 12% (4 of 33) of patients without cirrhosis relapsed after 6 weeks of treatment and 7% of (2 of 30) of patients with cirrhosis relapsed after 8 weeks of treatment. Among both groups of treatment-experienced patients receiving 12 weeks of treatment, only one virologic failure was observed: a 58-year-old white woman with genotype 3a HCV infection and cirrhosis, who had previously received unsuccessful treatment with sofosbuvir plus peginterferon and ribavirin. This patient, who had HCV RNA <15 IU/mL by week 2 of treatment, had virologic relapse by post-treatment week 8.

Baseline sequencing was available for 128 of the 128 patients enrolled in the study. Baseline RASs in at least 1 of the 3 target genes (NS3, NS5A, and NS5B) were detected by deep sequencing (1% cutoff) in 63 of the 128 patients: 54% (34 of 63) treatment-naïve, 26% (7 of 27) interferon-experienced, DAA-naïve, and 58% (22 of 38) of DAA-experienced patients (data not shown).

Table 3 shows the SVR rates for patients without RASs and with single and multi-class NS3, NS5A, and NS5B RASs with a 1% sequencing cutoff. In treatment-naïve patients, SVR rates with 8 weeks of treatment with sofosbuvir-velpatasvir plus GS-9857 were 92% (12 of 13) and 94%

Table 3. Sustained Virologic Response 12 Weeks After Treatment in Patients With and Without Baseline Resistance-Associated Substitutions (1% Sequencing Cutoff)

	Treatment-naïve		Treatment-experienced SOF-VEL plus GS-9857 for 12 wk	
	No cirrhosis	Cirrhosis		
Variable	SOF-VEL + GS-9857 for 6 wk (n = 33)	SOF-VEL + GS-9857 for 8 wk (n = 30)	No DAA(s) (n = 27)	DAA(s) (n = 38)
No RASs	12/12 (100)	16/17 (94)	20/20 (100)	16/16 (100)
Any RASs	17/21 (81)	12/13 (92)	7/7 (100)	21/22 (95)
NS3 RASs only[a]	2/2 (100)	1/1 (100)	2/2 (100)	3/3 (100)
NS5A RASs only	8/12 (67)	9/10 (90)	2/2 (100)	10/10 (100)
NS5B RASs only	2/2 (100)	1/1 (100)	0	3/3 (100)
Multiclass RASs[a]	5/5 (100)	1/1 (100)	0	5/6 (83.3)

NOTE. Values are n (%).
SOF, sofosbuvir; VEL, velpatasvir.
[a]Includes patients with the NS3 RAS Q80K.

(16 of 17) in patients with and without baseline RASs, respectively. A 15% sequencing cutoff demonstrates similar results (Supplementary Table 5).

Sequencing data are available for all 7 virologic failures. All 6 treatment-naïve patients had the same or fewer to no RASs detected at time of relapse. The 1 DAA-experienced patient with genotype 3a who experienced virologic failure had the NS5A RAS Y93H at baseline and relapse and had treatment-emergent NS3 RAS Q80R (41%), which does not confer in vitro resistance to GS-9857 (confers 0.8-fold shift in 50% effective concentration in genotype 3a replicon assays).

Most patients in all 4 groups had at least 1 adverse event (Table 4). The most common events were headache, diarrhea, fatigue, and nausea. All but 3 adverse events were mild to moderate in severity. The only serious adverse event reported was gastroenteritis in a treatment-experienced patient with cirrhosis who received 12 weeks of treatment.

Three patients discontinued treatment due to adverse events: 2 treatment-naïve and 1 treatment-experienced patient. All 3 had cirrhosis. One of the treatment-naïve patients, a 76-year-old Asian woman, discontinued treatment of her own accord due to fatigue on day 36, and the other, a 64-year-old white woman, had her treatment discontinued by the investigator on day 49 due to exacerbation of diarrhea, vomiting, weakness, and dehydration. The single treatment-experienced patient was a 59-year-old black woman who discontinued study treatment of her own accord after experiencing gastritis on day 64 of treatment. The adverse events of fatigue and gastritis were considered unrelated to study drug by the investigator. All 3 patients who discontinued therapy achieved SVR12.

One patient died during follow-up. This patient, a treatment-experienced 59-year-old man with genotype 2b HCV infection without cirrhosis and no cardiac medical history, died at during post-treatment follow-up week 14. On the evening before his death, he reported vague epigastric pain and was found dead the next morning, presumed to have sudden cardiac death. No autopsy report is available.

The rates of clinically significant laboratory abnormalities were low: 5 patients (4%) had grade 3 abnormalities and 4 (3%) had grade 4 abnormalities. One patient had a grade 4 elevated level of creatine kinase during a follow-up visit. According to the investigator, this patient, a 34-year-old white man without cirrhosis who received 6 weeks of treatment, had exercised vigorously before the visit. The only laboratory abnormalities observed in more than 1 patient were asymptomatic and transient grade 3 and 4 lipase elevations.

Discussion

With the recent approval of DAAs, safe and effective combination regimens are now available for the majority of

Table 4. Safety

Variable	Treatment-naïve		Treatment-experienced	
	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
	SOF-VEL + GS-9857 for 6 wk (n = 33)	SOF-VEL + GS-9857 for 8 wk (n = 30)	SOF-VEL + GS-9857 for 12 wk (n = 36)	SOF-VEL + GS-9857 for 12 wk (n = 29)
Any AE	23 (70)	20 (67)	27 (75)	25 (86)
Serious AEs	0	0	0	1 (3)
AEs leading to treatment discontinuation	0	2 (7)	0	1 (3)
Deaths	0	0	1 (3)	0
AEs (occurring in ≥5% of patients of any cohort)				
Headache	10 (30)	3 (10)	11 (31)	8 (28)
Diarrhea	10 (30)	1 (3)	10 (28)	8 (28)
Fatigue	7 (21)	3 (10)	10 (28)	6 (21)
Nausea	9 (27)	3 (10)	8 (22)	4 (14)
Constipation	1 (3)	2 (7)	2 (6)	1 (3)
Dizziness	3 (9)	0	0	3 (10)
Dry mouth	2 (6)	1 (3)	0	3 (10)
Abdominal pain, upper	2 (6)	1 (3)	1 (3)	1 (3)
Nasopharyngitis	1 (3)	1 (3)	0	3 (10)
Upper respiratory tract infection	2 (6)	1 (3)	1 (3)	1 (3)
Laboratory abnormalities				
Hemoglobin, 7.0 to <9.0 g/dL	0	0	0	1 (3)
Neutrophils, 500 to <750/mm^3	1 (3)	0	0	0
Platelets, 25,000 to <50,000/mm^3	0	0	0	1 (3)
Creatine kinase, ≥20.0 × ULN	1 (3)	0	0	0
Hyperglycemia, 30 to <40 mg/dL	0	0	1 (3)	0
Lipase, <3.0 × ULN	0	1 (3)	0	3 (10)

NOTE. Values are n (%).
AE, adverse event; SOF, sofosbuvir; ULN, upper limit of normal; VEL, velpatasvir.

patients chronically infected with HCV. SVR rates exceeding 90% can be achieved in most patient populations regardless of genotype, treatment experience, or presence of cirrhosis. Although the proportion of patients who do not achieve SVR with currently approved DAA regimens is small, the absolute number of DAA failures will steadily increase in parallel with the rate of treatment uptake. DAA failures represent an unmet medical need without, at this time, any approved retreatment options. In this open-label, phase 2 study, the combination of sofosbuvir-velpatasvir plus GS-9857 for 12 weeks was safe and highly effective for the treatment of patients with genotypes 2, 3, 4, or 6 HCV infection with or without compensated cirrhosis who were treatment-experienced, including those who had failed previous DAA regimens. The high SVR12 rate among treatment-experienced patients with genotype 3 HCV infection and cirrhosis is noteworthy, given the lower SVR12 rates generally experienced by this patient population.

Currently approved regimens for non-genotype 1 HCV have durations of 12–24 weeks, depending on choice of regimen and patient's baseline characteristics, such as HCV genotype, treatment history, and presence or absence of cirrhosis. The feasibility of shortening the duration of treatment has been a goal of research, especially for non-ribavirin-containing regimens. Several trials have evaluated various combinations of DAAs for 4 weeks, but with uniformly disappointing outcomes—SVR12 rates of 20% to 40%.[17,20,21] In this trial, 6 weeks of sofosbuvir-velpatasvir plus GS-9857 achieved suboptimal results (<90% SVR12 rate) in a historically easy-to-treat population of treatment-naïve patients without cirrhosis. Eight weeks of sofosbuvir-velpatasvir plus GS-9857 was safe and effective for treatment-naïve patients with cirrhosis, including those with HCV genotype 3. Thus, the 8-week regimen may serve as a shorter-duration option for treatment-naïve patients with or without cirrhosis and is currently being evaluated in phase 3 clinical trials.

Additionally, the high SVR12 rates across genotypes suggest the pangenotypic treatment potential of sofosbuvir-velpatasvir plus GS-9857. Although genotype 1 patients were not treated in this study, a parallel open-label, phase 2 study of patients infected with HCV genotype 1 was also conducted, where patients received treatment for 6–12 weeks.

This study was limited by its small sample size and open-label design. Although the first phase 2 clinical trial to evaluate retreatment of non-genotype 1 HCV-infected patients previously treated with DAA-regimens that included NS5A inhibitors, only 6 patients in this subgroup were enrolled. Also, no patients with genotype 5 HCV and only 3 patients with genotype 6 HCV were enrolled, reflecting the low prevalence of these infections in North America and New Zealand.

In conclusion, sofosbuvir-velpatasvir plus GS-9857 is a safe and effective treatment in patients with HCV genotypes 2, 3, 4, and 6, with and without compensated cirrhosis. High SVR rates were achieved in treatment-experienced patients, including those with DAA experience, after 12 weeks of sofosbuvir-velpatasvir plus GS-9857 and in treatment-naïve patients with compensated cirrhosis after 8 weeks of this regimen. These 3 potent pangenotypic DAAs have been co-formulated into a fixed-dose combination tablet. The phase 3 program will evaluate this fixed-dose combination for 8 weeks in treatment-naïve patients of all genotypes and for 12 weeks in patients of all genotypes who had received previous treatment with a DAA.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.07.038.

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Conflicts of interest
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